Definitive Chemoradiation in Oligometastatic Squamous Cell Carcinoma of the Anal Canal

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CASE REPORTS

We describe the treatment courses in 5 cases of isolated metastatic squamous cell carcinoma of the anal canal (SCCAC). In 4 of the 5 cases, the patients presented with metachronous metastatic recurrence after treatment for localized early-stage disease. The remaining patient presented with metastatic disease at initial diagnosis.

Case 1

Approximately 4 years after chemoradiation with 5-fluorouracil (5-FU) and cisplatin for a localized T2N3M0 SCCA, a 70-year-old man was found to have an enlarged left supraclavicular lymph node on a routine surveillance scan. A computed tomography (CT)–guided biopsy was performed, and pathology confirmed SCCAC. An induction chemotherapy regimen was initiated of 5-FU 750 mg/m^2 per day by continuous intravenous (IV) infusion on days 1–5, plus cisplatin 75 mg/m^2 IV on day 1 every 28 days for 2 cycles. Restaging CT scans demonstrated a slight decrease in size (from 1.6 × 1 to 1.4 × 1 cm) of the metastatic left supraclavicular lymph node, with no new sites of disease. The patient went on to receive chemoradiation with concurrent continuous IV infusion of 5-FU 300 mg/m^2 per day on the days of radiation. Intensity-modulated radiation therapy (IMRT) was delivered at a dose of 63 Gy in 28 fractions to the left supraclavicular node and 50.4 Gy in 28 fractions to the adjacent lymphatic region. 5-FU alone was given with the radiation because of the patient's poor tolerance of cisplatin during induction chemotherapy. He was observed in routine surveillance. Fifteen months after completion of chemoradiation therapy, he developed a new para-aortic lymph node just below the left renal hilum measuring 1.5 × 1.8 cm, with biopsy confirming SCCAC (Figure 1). Once again, chemoradiation was initiated. IMRT at a dose of 63 Gy over 30 fractions was administered to the para-aortic lymph node concurrently with continuous IV infusion of 5-FU 300 mg/m^2 per day on the days of radiation. Thirty-two months after this course of chemoradiation, the patient was without evidence of disease recurrence (Figures 2 and 3).

Case 2

A 62-year-old woman with SCCAC was treated with chemoradiation with 5-FU and mitomycin-C. One year later, she was found to have a lesion in the left lateral segment of the liver. She underwent liver segmentectomy and cholecystectomy. Pathology revealed SCC. She received 5-FU 1000 mg/m^2 per day by continuous infusion on days 1–4 and cisplatin 75 mg/m^2 IV on day 1 every 28 days for 4 cycles as adjuvant chemotherapy. Five months after adjuvant chemotherapy, a positron emission tomographic (PET)/CT scan showed a new focal fluorodeoxyglucose (FDG)-avid lesion in the right lobe of the liver and an FDG-avid focus in the porta hepatis, consistent with metastatic disease. At that time, she reported to our institution for recommenda-

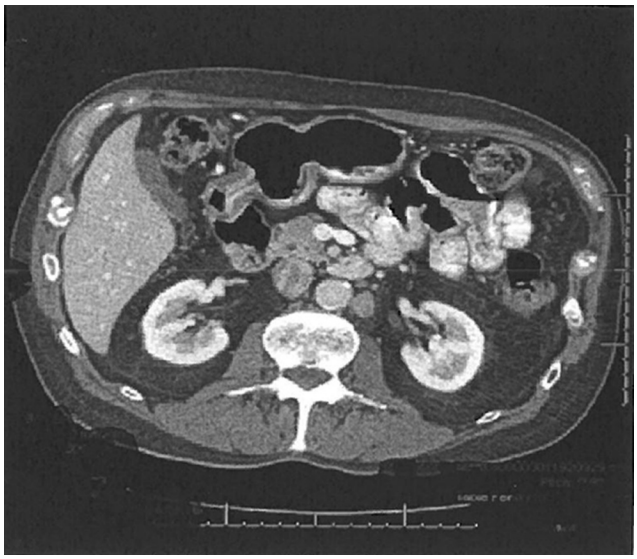

Figure 1. Case 1: para-aortic lymph node before chemoradiation.

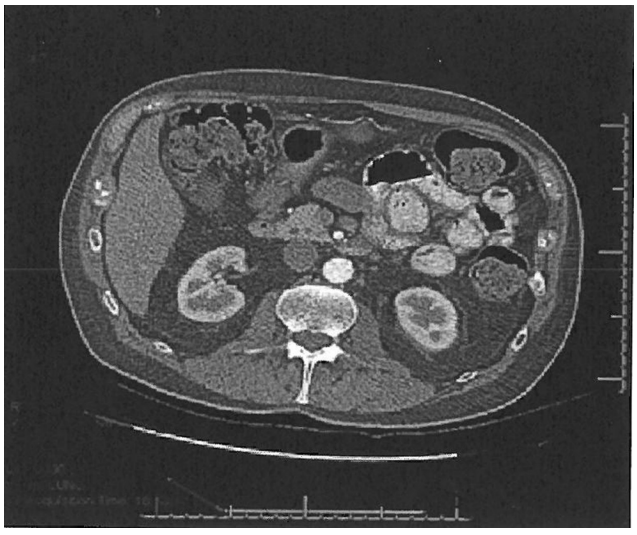

Figure 2. Case 1: para-aortic lymph node as in Figure 1, 2 months after chemoradiation.

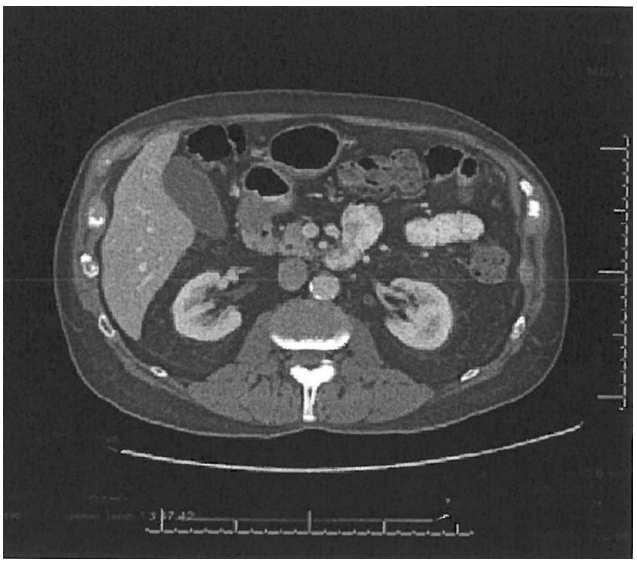

Figure 3. Case 1: most recent CT scan.

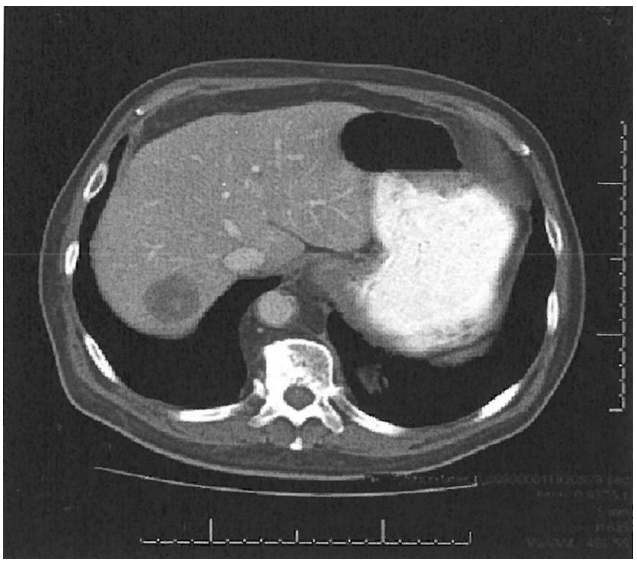

Figure 4. Case 4: liver lesion before chemoradiation.

tions. CT of the chest, abdomen, and pelvis indicated a 3.0 × 2.2-cm metastasis within the right hepatic lobe and a 3.3 × 2.1-cm peripancreatic/periportal nodular metastasis, with no evidence of disease in the chest. She was given concurrent definitive chemoradiation: IMRT, with a dose of 54 Gy in 27 fractions to the liver and periportal lymph node, along with oral capecitabine 1650 mg/m^2 on the days of radiation. Six months after chemoradiation, an 8-mm lesion was found on restaging scans in the right lobe of the liver and she underwent radiofrequency ablation (RFA). Twenty-seven months later, she was without evidence of metastatic disease.

Case 3

A 43-year-old woman with T3N1M0 SCCAC was treated with chemoradiation with 5-FU and mitomycin-C and abdominoperineal resection (APR) because of limited response to chemoradiation treatment and 6 cycles of adjuvant chemotherapy with cetuximab and cisplatin. The decision in favor of adjuvant chemotherapy was based on the surgical pathology of close margins and positive lymph node involvement. Three months after completion of the adjuvant chemotherapy, imaging identified bilateral lung metastases. A CT of the chest, abdomen, and pelvis revealed a 1.4 × 1.3-cm right lower lobe nodule and an 8.5-mm left lower lobe nodule indicative of metastatic disease. The patient received 6 cycles of systemic chemotherapy with carboplatin and paclitaxel, with tumor response. This treatment was followed by a right lower lobectomy and left wedge resection of the pulmonary metastasis, with pathology consistent with SCC. Three months after this procedure, mediastinal adenopathy appeared and was observed for 3 months. At that time, a PET/CT scan revealed mediastinal lymphadenopathy with three mediastinal lesions that were PET positive, suggestive of progressive disease. The patient presented to our institution for further recommendations. Induction chemotherapy was administered, with carboplatin, paclitaxel, and cetuximab for three cycles, and the lesions responded, with the left subhilar lymph node now measuring 1.4 × 1.0 cm compared with 2.0 × 1.5 cm previously and two remaining subcentimeter lymph nodes in the middle compartment of the mediastinum. Initiation of definitive chemoradiation to the left hilar lymphadenopathy and the suspicious mediastinal area was recommended. She underwent IMRT with a dose of 58 Gy in 25 fractions to the left hilar lymph node, 54 Gy in 25 fractions to the right mediastinal adenopathy, and 42 Gy in 25 fractions to the remaining mediastinal areas. The chemotherapy administered with the radiation included cisplatin 20 mg/m^2 IV weekly plus 5-FU 300 mg/m^2 per day by continuous IV infusion on the days of radiation. At this writing, 14 months had elapsed since chemoradiation, with no evidence of recurrent disease.

Case 4

An 80-year-old man developed an oligometastatic liver lesion 5 months after definitive chemoradiation with 5-FU and mitomycin-C for recurrent SCCAC. Two years before definitive chemoradiation to the primary tumor, a colonoscopy showed a small rectal polypoid area adjacent to an internal hemorrhoid. A biopsy confirmed invasive, poorly differentiated SCCAC with basaloid features. After diagnosis, however, the patient was lost to follow-up. Two years after the original finding, he underwent a flexible sigmoidoscopy that revealed a right anterior mass involving the internal anal sphincter biopsy that was positive for SCCAC with basaloid features, with CT imagining negative for metastatic disease. Definitive chemoradiation with 5-FU and mitomycin-C was initiated at another institution. During the course of radiation treatment, therapy was held for 3 weeks because of severe dehydration, diarrhea, radiation dermatitis, and neutropenia. The treatment was completed after the delay. Five months after chemoradiation, a CT of the abdomen and pelvis revealed a 3.5 × 3.2-cm mass in segment 8 of the liver (Figure 4). Chest imagining was negative. At this time, the patient reported to our institution for recommendations. Systemic chemotherapy was initiated with 5-FU, according to the de Gramount regimen. Single-agent 5-FU was given alone because of the patient's performance status, poor tolerance of previous 5-FU and mitomycin treatment, and comorbidities, including chronic renal insufficiency. After 4 cycles of 5-FU, an MRI revealed a decrease in the hepatic lesion to

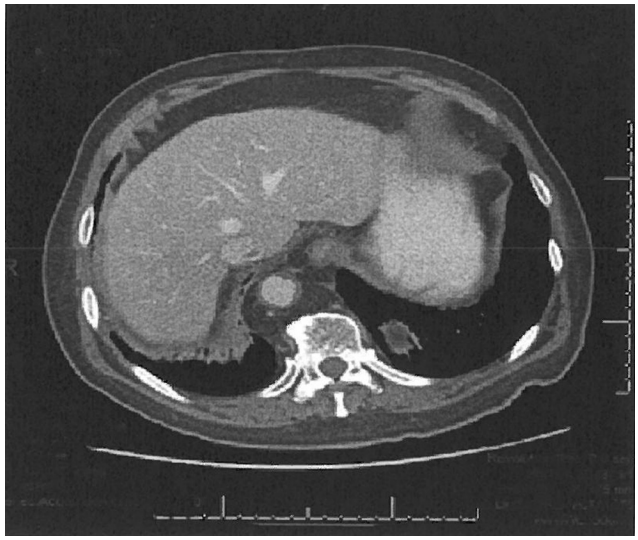

Figure 5. Case 4: most recent CT scan.

2.5 cm. Imagining was negative for other metastatic involvement. Chemoradiation was initiated to the solitary hepatic metastasis with infusional 5-FU. He underwent IMRT with a dose of 60 Gy in 30 fractions to the liver metastasis, along with 5-FU 300 mg/m^2 per day continuous infusion, on the days of radiation only. Fourteen months after definitive chemoradiation to the isolated liver metastasis, he remained in good health and without evidence of disease recurrence (Figure 5).

Case 5

At initial diagnosis, a 43-year-old woman presented to our institution with an 8-month history of rectal bleeding. Three months earlier, she had been found to have a mass at the entrance of the anus measuring 6 × 5 cm, with a biopsy showing infiltrating, moderately differentiated SCCAC. A CT scan of the abdomen and pelvis revealed 2, low, attenuated liver lesions suspicious for metastatic disease, measuring 1 and 5 cm, with a 3.7 × 2.7-cm right external iliac node. Chest imaging was negative. Systemic chemotherapy was initiated with 5-FU 750 mg/m^2 per day by continuous IV infusion on days 1–5, plus cisplatin 75 mg/m^2 IV on day 1 every 28 days. After 4 cycles, restaging scans showed stable disease. Definitive radiation was applied to the primary anal tumor and to the two small liver metastases, combined with capecitabine and cisplatin. The patient underwent an IMRT at a dose of 54 Gy in 27 fractions to the primary tumor and 50 Gy in 25 factions to the liver lesions, along with capecitabine 1400 mg/m^2 per day orally on the days of radiation therapy, plus weekly cisplatin 20 mg/m^2 IV during radiation. She remained disease free for 15 months after chemoradiation, but then was noted to develop bilateral lung metastases. At this writing, treatment with systemic chemotherapy has been reinitiated.

DISCUSSION

Anal cancer is a rare malignancy representing 2% of digestive system cancers.[1] Although anal cancer is still rare, the incidence is increasing, with an estimated 7060 new cases expected in 2013. SCC is the predominant histology, and most patients present with localized or locally advanced disease.[2,3] Treatment for nonmetastatic SCCAC consists of combined definitive chemoradiation therapy with 5-FU plus mitomycin-C or cisplatin. This approach is curative, with 5-year survival rates comparable to those with surgery, with APR and permanent colostomy reserved for patients found to have residual disease after chemoradiation.

Distant metastatic disease occurs in 10–20% of patients.[2] Common metastatic sites include distant lymph nodes, liver, and lungs, with less frequent sites including the peritoneum, bone, brain, and skin.[2,4] Among these patients, observed most often is metachronous metastatic disease recurrence after primary treatment for localized disease, whereas only 5% have metastatic disease at initial diagnosis.[2,3] With a small percentage of patients having metastatic disease, no phase III trials are available that are dedicated to the metastatic setting to help guide treatment decisions. Most treatment strategies are based on retrospective case studies, experience, and data extrapolated from the more common SCC treatment experiences. A common practice is to use systemic platinum doublet combination chemotherapy, with or without epidermal growth factor receptor (EGFR) monoclonal antibodies, for symptom control and to prolong survival. Data are limited regarding localized treatment strategies, such as surgery, radiation, and a combined modality with chemotherapy. Five-year survival rates are reported at 18–21% for distant metastatic SCCAC.[5,6]

There is limited experience with localized treatment approaches in metastatic SCCAC. In a recent retrospective review at U. T. M. D. Anderson, 77 patients with metastatic SCCAC treated with platinum-based combined chemotherapy were evaluated.[4] Median overall survival in all the patients was 29 months, with median progression-free survival of 6 months. Patients who received combined-modality treatment (chemotherapy, metastasectomy, radiation, or all 3) had an improved median overall survival of 35 months, compared with those treated with chemotherapy alone. Further, a study described 6 SCCAC cases with para-aortic lymph node involvement treated with chemoradiation. This study showed 3-year actuarial rates of 100% for locoregional control, 56% for distant control, and 63% for overall survival.[7] Hepatic resection for SCCAC to the liver has also been described. In a study evaluating liver-directed therapy for SCC with liver metastasis, 27 of 52 patients had anal primary SCC.[8] Outcomes for this subset showed median disease-free survival of 9.6 months and 5-year overall survival of 23%. In addition, case reports have described long-term, disease-free intervals in patients who have undergone local therapy for metastatic SCCAC.[9,10] These findings indicate a potential benefit for definitive combined-modality therapy in select patients with SCCAC with distant disease.

CONCLUSION

We report 5 cases with a variety of oligometastatic SCCAC sites treated with definitive chemoradiation therapy. In 4 of the 5 cases, the patients received systemic chemotherapy, with or without an EGFR monoclonal antibody for metastatic disease before chemoradiation, with evidence of disease stability or response to therapy. These 5 patients have had significant disease-free intervals ranging from 14–32 months. In 4 patients, the disease-free intervals at this writing were longer than the prior disease-free intervals, suggesting that all of the oligometastatic disease has been effectively treated. Further data are needed to define the outcomes of this approach.

However, because of the highly sensitive nature of localized SCCAC to chemoradiation, it makes sense to consider combined-modality therapy as a potential treatment option for select patients with isolated metastatic disease. Such treatment may result in a reasonable disease-free interval without subjecting the patients to full-dose systemic chemotherapy and additional toxicity.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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